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Clinicopathological characteristics and prognostic factors of ovarian granulosa cell tumors: A JSGO-JSOG joint study

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Abstract

Objectives: The aim of this study was to elucidate the clinicopathological features of ovarian granulosa cell tumors (GCTs) and to identify the prognostic factors.

Methods: The Japanese Society of Gynecologic Oncology (JSGO) conducted an observational retrospective cohort study of women with GCTs enrolled in the Gynecological Tumor Registry of the Japan Society of Obstetrics and Gynecology (JSOG) between 2002 and 2015. Clinicopathological features, including lymph node metastasis, were evaluated. In addition, we performed a prognostic analysis of patients between 2002 and 2011 for whom survival data were available. Kaplan–Meier and multivariate Cox proportional hazards analyses were performed.

Results: We identified 1426 patients with GCT. Of the 222 patients who underwent lymph node dissection, 10 (4.5%) had lymph node metastasis. The incidence of lymph node metastasis in patients with pT1, pT2, and pT3 was 2.1%, 13.3%, and 26.7%, respectively ($p<0.001$). Prognostic analysis was performed on 674 patients. In the multivariate Cox regression analysis, residual disease after initial surgery (hazard ratio (HR)=10.39, 95% confidence interval (CI)=3.15–34.29) and lymph node metastasis (HR=5.58, 95% CI=1.62–19.19) were independent risk factors for cancer-specific survival.

Conclusions: In the initial surgery for GCTs, lymph node dissection can be omitted if the operative finding is pT1. In cases of pT2 or higher, lymph node dissection should be

considered. Debulking is critical for achieving no gross residual tumor at the end of the surgery.

Keywords: lymph node metastasis; ovarian granulosa cell tumor; prognosis; surgery

1. Introduction

Granulosa cell tumors (GCTs) are tumors that constitute 2–5% of malignant ovarian cancers [1]. These tumors are often characterized by later recurrences > 5 or 10 years after initial treatment [2,3]. Because of their low incidence, many studies group combined GCTs with other sex cord-stromal tumors (SLCTs) such as Sertoli-Leydig cell tumors in their assessments [4–7]. It has been reported that 97% of these tumors have somatic mutations in the *FOXL2* gene [8], elucidating the unique mutational profile of these tumors. For this reason, it is important to conduct research that specifically targets GCTs.

However, there is a lack of robust evidence from clinical trials regarding the treatment of GCTs. Because stage I cases account for 64% to 89% of all cases [9–11], the primary treatment is mainly surgical. The purpose of surgery in the initial treatment of ovarian cancer is to diagnose the histological type and extent of tumor involvement and to remove the primary and metastatic lesions as much as possible. Despite the different histological origin of the tumor, the surgical treatment strategy, including whether to perform lymph node dissection, is in accordance with the guidelines for epithelial ovarian cancers.

Therefore, the primary objective of this study was to elucidate the clinicopathological features of GCTs using bulky data from Japan's nationwide registry. The second objective was to identify the prognostic factors for GCTs.

2. Materials and Methods

2.1. Data sources for the study

This observational retrospective study used the Gynecologic Tumor Registry database of the Japan Society of Obstetrics and Gynecology (JSOG), a nationwide project undertaken by the Japanese Society of Gynecologic Oncology (JSGO). The dataset was provided by the Gynecologic Oncology Committee of JSOG in 2018, and the study was a collaboration between JSGO and JSOG. The JSOG database is an organ-based cancer registry for gynecologic malignancies that records comprehensive information on cancer types, properties of the tumor, therapeutic categories, and survival profile. The ovarian tumor registry has been conducted annually by the Gynecologic Tumor Committee of JSOG since 2002. The registry comprises 466 hospitals, which account for approximately 50% of all new cases with gynecologic malignancies in Japan. The JSGO database focuses on the leading hospitals in Japan, such as university hospitals and cancer centers. The data in the present study were mainly from surgeries and treatments performed by gynecologic oncologists certified by the JSGO. Institutional review board approval was obtained from the Clinical

Research Committee of JSOG (2018-36-67) and the hosting institution, Tokai University School of Medicine (17R-100).

2.2. Patients

Histopathological classification codes (B11-00) were applied to specify the GCTs in the database. Women with GCTs who underwent initial treatment between 2002 and 2015 were included in this study. Patients with unknown stage, those who had not undergone surgery, and those who did not have an ovarian primary tumor were excluded. Among the cases that met the inclusion criteria, patient age, FIGO stage, procedures in the initial surgery (hysterectomy, salpingo-oophorectomy, and lymph node dissection), residual disease after initial surgery (no gross residual disease, residual tumor diameter ≤1 cm, diameter 1–2 cm, or >2 cm), neoadjuvant chemotherapy, and adjuvant chemotherapy were extracted from the database. The recorded cancer stage was classified based on the 1988 International Federation of Gynecology and Obstetrics (FIGO). Surgical procedures were registered as biopsy only, unilateral salpingo-oophorectomy, bilateral salpingo-oophorectomy, salpingo-oophorectomy in conjunction with total hysterectomy, or tumor removal from some other organ. In this registry, no distinction was made between unilateral salpingo-oophorectomy and cystectomy (tumor resection). Similarly, we did not distinguish between open and laparoscopic surgery in the registry. According to the findings of the laparotomy and the histological findings of the removed specimen, each case was registered

using the pathological tumor node metastasis (pTNM) classification. In the JSOG gynecologic tumor registry, the system is designed to register patients in the year of their initial treatment and to provide prognostic reports three and five years later. At the time the dataset was provided, survival information of the treated cases was included from 2002 to 2011. Survival outcomes were duration of follow-up, status of living, and cause of death. Cancer-specific survival (CSS) was determined to be the period from diagnosis to death caused by ovarian cancer. Cases without survival events or untraceable cases were censored at the last visit with a known life condition.

2.3. Statistical analyses

Continuous variables are described as median and interquartile range (IQR). For categorical variables, statistical differences were assessed using the chi-square test or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to form survival curves, and the differences between the curves were assessed with the log-rank test. In addition, the Cox proportional hazard regression model was used for multivariate analysis using the step-down method with variables that were statistically significant in the univariate analysis. The magnitude of statistical significance was expressed as hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were based on a two-sided hypothesis, and statistical significance was set at $p<0.05$. SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) was used for all analyses. The Strengthening the Reporting of

Observational Studies in Epidemiology (STROBE) guidelines were consulted to display the results according to an observational cohort study [12].

3. Results

The patient selection schema is shown in Figure 1. There were 75,241 women with ovarian malignancies documented in the JSOG Gynecologic Tumor Registry during the study period. Granulosa cell histology was observed in 1,435 women. The final study population comprised 1,426 (1.9%) women with ovarian GCTs.

3.1. Analysis of clinicopathological factors

The demographical and clinicopathological characteristics of the patients are summarized in Table 1. The median (IQR) age was 55 (43–66) years. A total of 876 (61.4%) patients were over 50 years of age. The majority of GCTs were classified as FIGO stage I disease (89.1%). All the patients underwent surgical treatment. None of the GCT patients received neoadjuvant chemotherapy. A total of 1,045 women (73.3%) underwent surgical procedures including bilateral salpingo-oophorectomy and/or hysterectomy, whereas 339 (23.8%) underwent unilateral salpingo-oophorectomy or tumor resection. The rate of complete gross resection in the initial surgery was 93.0%. A total of 222 patients (15.6%) underwent lymph node dissection and 201 patients (14.2%) received adjuvant chemotherapy. A higher stage (II–IV) was associated with more frequent adjuvant

chemotherapy use (9.0% chemotherapy use for stage I and 55.5% for stage II–IV, p<0.001).

Of the 222 patients who underwent lymph node dissection, 10 (4.5%) had histologically confirmed lymph node metastasis. The rates of lymph node metastasis in patients with pT1, pT2, and pT3 were 2.1%, 13.3%, and 26.7%, respectively (p<0.001). There were no pT3a cases in which lymph node dissection was performed. These pT3 cases were either pT3b or pT3c (Table 2). The percentage of positive lymph nodes associated with the extent of lymph node dissection was 5.0% (7/139 cases) in patients with pelvic lymph node dissection only, 3.8% (3/79 cases) in patients with dissection of pelvic and para-aortic lymph nodes, and 0% (0/4 cases) in patients with dissection of para-aortic lymph nodes only.

3.2. Survival analysis

We performed a survival analysis of 674 patients who were initially treated between 2002 and 2011 (Fig. 1). The median (IQR) follow-up time for the cohort was 51.0 (41.4–65.5) months. Kaplan–Meier curves illustrate CSS (Fig. 2). CSS differed significantly according to the FIGO stage (p<0.001), residual disease after initial surgery (p<0.001), and lymph node status (p<0.001). The 5-year CSS rates for patients with FIGO stage I, II, III, and IV disease were 98.2%, 89.3%, 81.0%, and 66.7%, respectively (Fig. 2-A). The 5-year CSS for patients with no macroscopic residual disease, a residual disease diameter <1 cm, and residual disease diameter >1 cm were 97.9%, 74.1%, and 33.3%, respectively (Fig. 2-B). The three

groups were compared for lymph node status. The 5-year CSS rates for patients negative for metastasis, no node resection, and positive for metastasis were 97.4%, 96.9%, and 60.0%, respectively (Fig. 2-C). In contrast, there was no significant CSS rate difference according to age at diagnosis (<50 years vs. ≥ 50 years) (Supplementary Figure 1A), and lymph node dissection (with vs. without) (Supplementary Figure 1B). In the multivariate Cox regression analysis, residual disease after initial surgery (HR=10.39, 95% CI=3.15–34.29), and lymph node metastasis (HR=5.58, 95% CI=1.62–19.19) were independent risk factors for CSS (Table 3).

In addition, advanced cases of stage II and above (n=86) were examined. CSS differed significantly according to residual disease after initial surgery ($p<0.001$) (Supplementary Figure 2A). However, there was no difference in CSS between patients with and without adjuvant chemotherapy (Supplementary Figure 2B). On the other hand, there was no difference in CSS according to whether lymph node dissection was performed or not in the examined patients with stage pT1 (Supplementary Figure 3).

Furthermore, when patients aged 18 to 49 years with a FIGO stage I GCTs (n=243) were evaluated, the median (IQR) follow-up was 50.9 (41.1 to 65.6) months. There was no difference in CSS between fertility-sparing surgical procedures (unilateral salpingo-oophorectomy or tumor resection) and fertility-loss surgery including bilateral salpingo-oophorectomy and/or hysterectomy ($p=0.828$) (Fig. 3).

4. Discussion

The present study is the second-largest cohort study of GCTs following the study conducted by Seagle et al. [11]. Our study demonstrated that lymph node metastasis in GCTs was positively associated with the macroscopic findings at laparotomy, and residual tumor and lymph node metastasis at the initial surgery were poor prognostic factors.

Previous reports have shown that the incidence of lymph node metastasis in GCTs is not very high. There are reports of 13 cases [13], 25 cases [14], and 36 cases [15] of GCTs with lymph node dissection and no positive metastases. In another report, 34 cases [7] and 47 cases of SCST were dissected without metastasis [5] and these papers concluded that lymph node dissection can be omitted because positive node frequency is extremely low. However, in a subsequent study with more patients, lymph node metastasis was found in 3.1% (42/1350) [11] and 3.3% (19/572) [6]. In our study, the results were identical, with metastasis observed in 4.2% (10/222). For the first time, we revealed that the incidence of lymph node metastasis was positively associated with pT classification. For stage pT1 cases, lymph node dissection was performed in 192 (14.9%) cases, but metastasis was as low as 2.1%. The combined metastatic rates of pT1 and pT2 remained low at 2.9%. This was considerably lower than the 14.2% observed in FIGO stage I and II epithelial ovarian cancer [16]. However, the incidence was higher in pT3 stage cases (26.7%), which was also

in accordance with previous reports of GCTs [11]. Therefore, based on the macroscopic findings at the time of laparotomy, it may be possible to predict the risk of lymph node metastasis. Seagle et al. [11] found that the non-dissected group had as poor a prognosis as the metastasis-positive group. Conversely, in our study, the non-dissected group had the same outcome as the node-negative group. This was probably due to the proportion of FIGO stage I cases being much more common in our study compared to Seagle et al.'s [11] group. Furthermore, analysis of pT1 cases only revealed that there was no difference in CSS between patients with and without lymph node dissection.

The prognosis is poor for cases with a FIGO stage II [10,17] or III [18,19] and patients over 50 years of age [19]; the existence of residual tumors and large tumor size are also poor prognostic factors [9]. In cases of incomplete staging, recurrence is more frequent [14]. In our study, the FIGO stage was a prognostic factor in the univariate analysis. However, a multivariate analysis showed two selections: residual tumor at surgery and histologically confirmed lymph node metastasis. Conversely, in stage I, which accounts for most cases, the prognosis is poor in the IC stage [20,21], tumor rupture [3,20], incomplete surgery [11], and non-staging surgery [21]. GCTs have been reported to have higher genomic stability than epithelial ovarian cancers [22,23] and *FOXL2* mutations are highly prevalent in both primary and metastatic lesions as well as in recurrent disease [24]. Therefore, Seagle et al. [11] proposed the possibility of de novo GCTs in the residual ovary

of some lesions that had been considered in late recurrence. According to a study of metastatic sites, pelvic and intra-abdominal recurrences were more prevalent, with only 5.7% of recurrences in lymph nodes alone [25]. This information would help explore therapeutic strategies.

The feasibility of fertility-sparing surgery has been reported as follows: Fertility-sparing surgery is associated with no difference in disease-free survival for stage I GCT patients under 50 years of age. In this study, fertility-sparing surgery is defined as the preservation of the uterus and at least one ovary [26]. We also compared the surgical procedures using the same definition and found no difference in CSS. However, Wang et al. [26] cautioned that recurrence is more common in cases with incomplete staging in the fertility-sparing group. In a study of stage I SCST in patients aged 18-49 years, fertility-sparing surgery was carefully performed because of its inferiority for CSS, although there was no difference in overall survival [27].

. The strength of our study is that it was a nationwide survey and had the second-largest sample size in the literature [11]. In this study, no ethnic information was requested at the time of registration. However, since foreigners account for only 1.7% of Japan's population, and most of them are from Asian countries, the JSOG data cover predominantly Asian patients [28]. Therefore, this study can be considered the largest cohort study in Asia. In addition, the JSGO database focuses on the leading hospitals in Japan, such as university

hospitals and cancer centers. The data in the present study were mainly from surgeries and treatments performed by gynecologic oncologists. The present study had some limitations. First, juvenile granulosa cell tumors were not registered separately, nor was there a centralized pathology review. Second, for comprehensive surgical staging, there was no data on each staging element (e.g., peritoneal washings, omentectomy, peritoneal biopsies) because it is not a registry category. Third, data on the timing of relapse and the pattern of recurrence have not been registered, so they are not available for investigation.

The following conclusions can be made based on the results of the present study: At the time of the initial surgery, lymph node dissection can be omitted if the surgical findings are pT1 after a thorough exploration of the abdominal cavity. In cases of pT2 or higher, lymph node dissection should be considered. Debulking is also important to ensure that there is no gross residual tumor at the end of the initial surgery. However, fertility-sparing surgery may be considered in FIGO stage I cases, although even in these cases, staging procedures such as inspection of the abdominal cavity and biopsy of the greater omentum and peritoneum are required.

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Conflict of Interests

No potential conflict of interest relevant to this article was reported.

Author contributions

Study concept and design: YE and MM; acquisition of data: YE, WY, TT, MK, and SN; analysis and interpretation of data: YE and MM; drafting of the manuscript: YE; Critical revision of the manuscript for important intellectual content: YE, TE, and MM. Final approval of manuscript: all authors.

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Figure Captions

Fig. 1 Flow chart of the patients included in the study

JSOG, Japan Society of Obstetrics and Gynecology

Fig. 2 Cancer-specific survival of patients with granulosa cell tumors by (A) FIGO stage, (B) residual disease after initial surgery, and (C) lymph node states

FIGO, International Federation of Gynecology and Obstetrics

Fig. 3 Cancer-specific survival of women aged 18 to 49 years with FIGO stage I granulosa cell tumors by surgical procedure

BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy

Supplementary Fig. 1 Cancer-specific survival of patients with granulosa cell tumors by (A) age at diagnosis and (B) lymph node dissection.

Supplementary Fig. 2 Cancer-specific survival of patients with advanced (stage II-IV) granulosa cell tumors by (A) residual disease after initial surgery and (B) adjuvant chemotherapy.

Supplementary Fig. 3 Cancer-specific survival of patients with pT1 granulosa cell tumors by lymphadenectomy.

Fig. 1

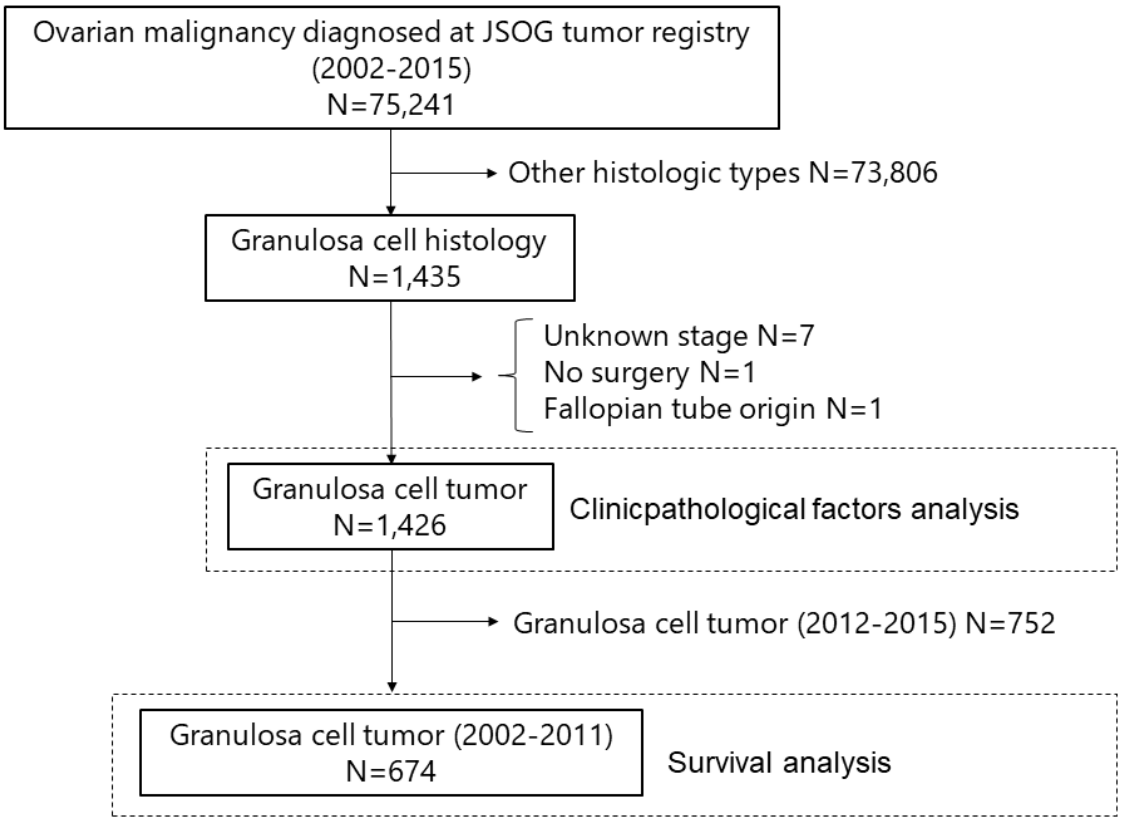

Ovarian malignancy diagnosed at JSOG tumor registry
(2002-2015)
N=75,241
Other histologic types N=73,806
Granulosa cell histology
N=1,435
Unknown stage N=7
No surgery N=1
Fallopian tube origin N=1
Granulosa cell tumor
N=1,426
Clinicpathological factors analysis
Granulosa cell tumor (2012-2015) N=752
Granulosa cell tumor (2002-2011)
N=674
Survival analysis

Fig. 2

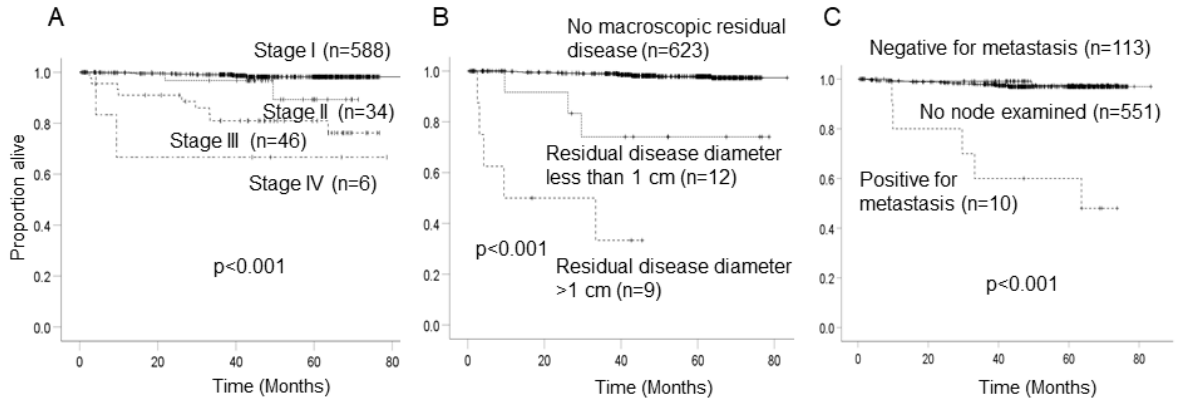
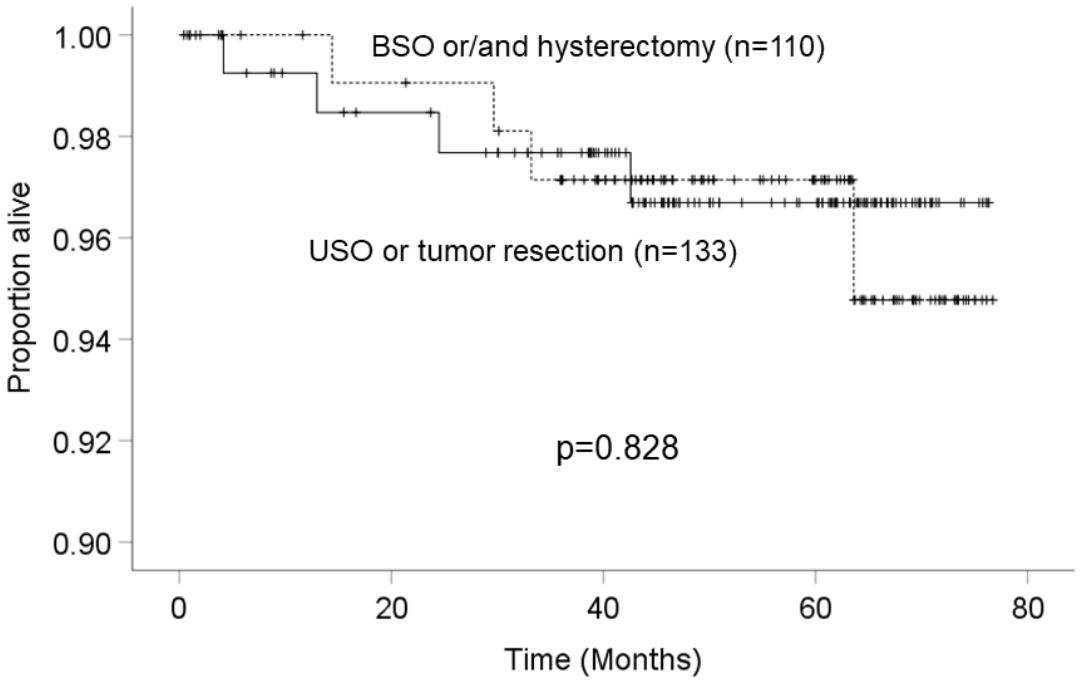
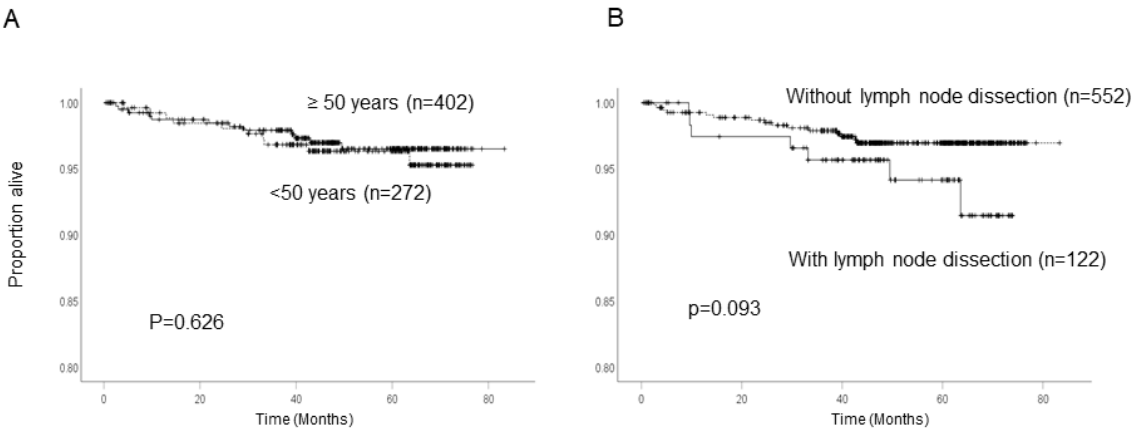

A
Stage I (n=588)
Stage II (n=34)
Stage III (n=46)
Stage IV (n=6)
p<0.001
Proportion alive
Time (Months)
B
No macroscopic residual disease (n=623)
Residual disease diameter less than 1 cm (n=12)
p<0.001
Residual disease diameter >1 cm (n=9)
Time (Months)
C
Negative for metastasis (n=113)
No node examined (n=551)
Positive for metastasis (n=10)
p<0.001
Time (Months)

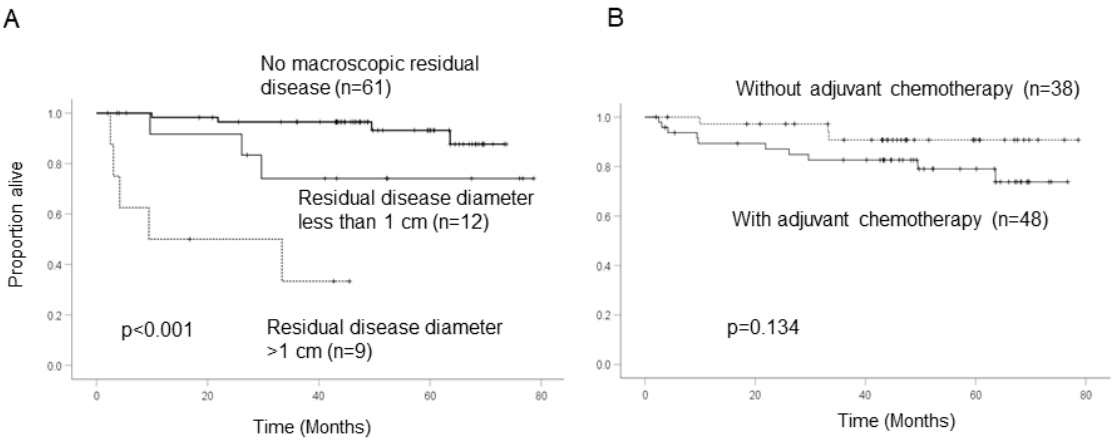
Fig. 3


1.00
0.98
0.96
0.94
0.92
0.90
Proportion alive
BSO or/and hysterectomy (n=110)
USO or tumor resection (n=133)
p=0.828
0
20
40
60
80
Time (Months)

Supplementary Fig. 1



Supplementary Fig. 2



Supplementary Fig. 3

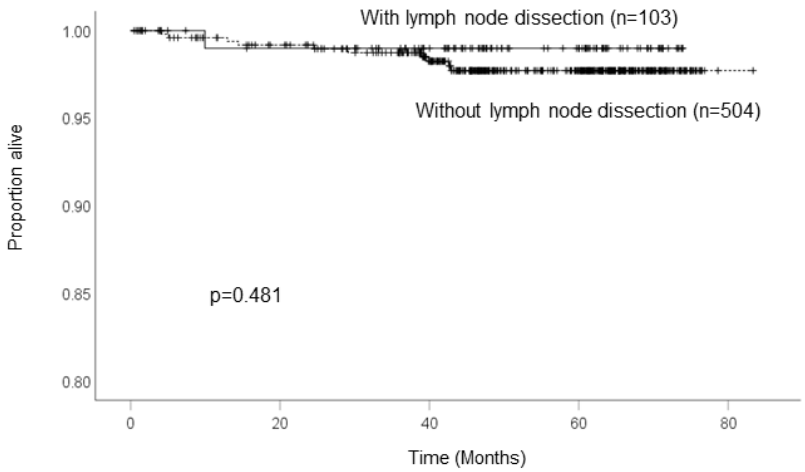


Table 1 Demographic and clinicopathological characteristics of patients with granulosa cell tumor

Age (years)			
<40		244	(17.1%)
40-49		306	(21.5%)
50-59		319	(22.4%)
60-69		310	(21.7%)
70≦		247	(17.3%)
Stage (FIGO 1988)			
I		1,271	(89.1%)
	IA	919	
	IB	13	
	IC	339	
II		66	(4.6%)
	IIA	6	
	IIB	19	
	IIC	41	
III		79	(5.5%)
	IIIA	7	
	IIIB	18	
	IIIC	54	
IV		10	(0.7%)
	IVA	2	
	IVB	8	
Operative procedure			
USO or tumor resection		339	(23.8%)
BSO or/and hysterectomy		1,045	(73.3%)
Other		42	(2.9%)
Lymph node dissection			
Yes		222	(15.6%)
	Pelvic	139	
	Pelvic and paraaortic	79	
	Paraaortic	4	
No		1,204	(84.4%)
Residual disease after initial surgery			
No		1,326	(93.0%)
Yes		44	(3.1%)

residual tumor diameter ≤1 cm	25	
residual tumor diameter 1–2 cm	4	
residual tumor diameter >2 cm	15	
Not reported	56	(3.9%)
Adjuvant chemotherapy		
Yes	201	(14.2%)
No	1,225	(85.8%)

USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy

Table 2 Lymph node metastasis rate by pTNM classification

pTNM classification	Number of cases of lymph node dissection	Number of histologically diagnosed metastasis-positive cases	Rate of metastasis
pT1	192	4	2.1% *
pT1a	121	2	1.7%
pT1b	3	0	0.0%
pT1c	68	2	2.9%
pT2	15	2	13.3% *
pT2a	1	0	0.0%
pT2b	5	0	0.0%
pT2c	9	2	22.2%
pT3	15	4	26.7% *
pT3a	0	-	-
pT3b	5	1	20.0%
pT3c	10	3	30.0%
total	222	10	4.5%

* $p<0.001$

pTNM, pathological tumor node metastasis

Table 3 Risk factors for cancer-specific survival of patients with granulosa cell tumor

Factors	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
FIGO stage		<0.001		0.082
I	1		1	
II-IV	10.74 (4.59-25.14)		3.12 (0.87-11.23)	
Residual disease after initial surgery		<0.001		<0.001
No macroscopic residual disease	1		1	
Positive	29.40 (11.57-69.71)		10.39 (3.15-34.29)	
Lymph node metastasis		<0.001		0.006
Negative or not examined	1		1	
Positive	21.15 (7.78-57.50)		5.58 (1.62-19.19)	

HR, hazard ratio; CI, confidence interval FIGO, International Federation of Gynecology and Obstetrics.